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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 08/634,039 | 04/17/1996 | DENIS P. SNIDER | 1038-588MIS/ | 8658 |

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| EXAMINER | |
|---|---|
| VANDERVEGT, FRANCOIS P | |
| **ART UNIT** | **PAPER NUMBER** |
| 1644 | |

DATE MAILED: 03/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

SM

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 08/634,039 | SNIDER, DENIS P. | |
| | Examiner | Art Unit | |
| | F. Pierre VanderVegt | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *09 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

The Examiner in charge of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to F. Pierre VanderVegt, Ph.D. in Art Unit 1644.

Claim 9 has been canceled.

Claims 1-8 are currently pending in this application and are the subject of examination in the present Office Action.

### *Response to Arguments*

1. In view of the Appeal Brief filed on August 28, 2003, PROSECUTION IS HEREBY REOPENED. New grounds of rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) request reinstatement of the appeal.

If reinstatement of the appeal is requested, such request must be accompanied by a supplemental appeal brief, but no new amendments, affidavits (37 CFR 1.130, 1.131 or 1.132) or other evidence are permitted. See 37 CFR 1.193(b)(2).

2. In view of the new grounds of rejection presented below, the present Office Action is made **NON-FINAL**. Applicant's arguments made in the Appeal Brief will be addressed as they pertain to the new ground of rejection.

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Wu et al (Infect. Immun. [1993] 61(1):314-322; 13 on form PTO-1449).

Wu teaches a method of immunizing animals with a protein antigen from a pathogenic organism, *Streptococcus mutans*, fused to cholera toxin B subunit. Wu teaches that immunization with the conjugate induces the production of antigen specific antibodies in the hosts, evidencing that the construct is recognized by professional antigen presenting cells and presented to CD4+ T cells which stimulate the humoral response [claims 1,2]. Wu teaches that nasal-associated lymphoid tissue in mice consist of follicles covered by domes of specialized epithelium resembling the M cells of Peyer's patches and comprise underlying lymphoid cells including CD4+ and CD8+ cells, with CD4+ cells predominating. Wu also teaches that in humans CD4+ cells outnumber CD8+ cells in the intraepithelial and submucosal lymphocytes of nasal mucosae, unlike in the intestinal mucosa where CD8+ cells predominate (page 320, first column in particular). The prior art teaching anticipates the claimed invention.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Estrada et al (Vaccine [1995] 13(10): 901-907; 38 on form PTO-1449) in view of Wu et al (Infect. Immun. [1993] 61(1):314-322; 13 on form PTO-1449) as evidenced by Hamaleers et al (Cell Tissue Res. [1989] 256:431-438; 14 on form PTO-1449).

The Estrada reference teaches immunization of subjects (hosts) via the intestinal mucosa using a peptide antigen [claim 4] covalently conjugated to anti-MHC Class II monoclonal antibodies (see entire document)[claims 2,3]. Estrada further teaches that these conjugates effectively induce production of IgA and IgG antibodies in mice (Abstract in particular)[claim 6]. Estrada also teaches that conjugation was effected via the hetero-bifunctional cross-linker SMPB (page 902, first column in particular)[claim 8].

Estrada teaches that the results indicate that immunotargeting complexes may be useful for oral vaccine delivery (page 902, top of first column in particular).

Estrada does not teach the intranasal administration of claims 1-8, the immunization with an antigen derived from a pahogen of claim 5 or the immunization of human hosts of claim 7.

Wu teaches a method of immunizing animals with a protein antigen from a pathogenic organism, *Streptococcus mutans*, fused to cholera toxin B subunit and teaches that intranasal immunization is an effective means of eliciting protective immunity (Abstract in particular)[claim 5]. Wu teaches both intragastric and intranasal administration (page 315, column 1 in particular). Wu teaches that, in similar immunizations, responses in saliva and serum were significantly stronger in intranasally immunized mice than in intragastric immunized mice. Wu teaches that nasal-associated lymphoid tissue in mice consist of follicles covered by domes of specialized epithelium resembling the M cells of Peyer's patches and comprise underlying lymphoid cells including CD4+ and CD8+ cells, with CD4+ cells predominating. Wu also teaches that in humans CD4+ cells outnumber CD8+ cells in the intraepithelial and submucosal lymphocytes of nasal mucosae, unlike in the intestinal mucosa where CD8+ cells predominate (page 320, first column in particular)[claim 7]. Wu further teaches that mice given antigen conjugates orally had antibody responses similar to intragastric administration, but much lower than intranasal (page 320, second new paragraph of first column in particular).

Hamaleers (Cell Tissue Res; hereafter Hamaleers CTR) teaches that in young mice "a few Ia+ cells" extend dendritic processes between dendritic processes between epithelial cells (page 434, second column in particular). Ia is well known in the art as the murine MHC class II antigen and is expressed exclusively on antigen presenting cells for presentation of antigenic peptides to CD4+ helper T cells, whose stimulation is part of the process for generating a humoral (antibody) response to antigen. Hamaleers CTR further teaches in the same paragraph, in agreement with Wu, "Ia antigen is also expressed on some epithelial cells. More Ia+ epithelial cells are seen as the animal grows older."

Applicant argues in the Appeal Brief filed December 9, 2003 that the results of Estrada obtained weak reactivity and that Estrada did not pursue this work in subsequent studies (page 5 of the Appeal Brief for example). Applicant further argues that there would be no motivation to combine the teachings of Estrada with those of Hamaleers ICB because Hamaleers CTR teaches that MHC class II is only poorly expressed by non-inflamed nasal epithelial cells in young rodents. Applicant is correct in the assertion about Hamaleers teachings regarding young rodents. However, as noted supra, that some Ia+ cells push dendritic processes between the epithelial cells and "[m]ore Ia+ epithelial cells are seen as the animal

grows older." The claims are not drawn to the treatment of young rodents specifically, rather hosts in general, human hosts in particular [claim 7].

It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to modify the immunization method of Estrada by replacing the intragastric administration of Estrada, proposed as a model for oral immunization, with the intranasal immunization of Wu using an antigen from a pathogenic organism. One would have been motivated to make the substitution with a reasonable expectation of success based upon the teachings by Wu that the NALT of the nasal mucosa is functionally similar to the PP of the intestines and the teachings of Estrada et al that the antibody conjugates specifically targeted the antigen presenting cells in the intestine. One would have been further motivated by the teachings of Wu that, unlike the PP, the lymphoid cells in the nasal mucosa are predominantly CD4+ and that nasal administration exceeded both gastric and oral administration in terms of humoral response. Lastly, one would have been further motivated to substitute the method of Wu based upon the general knowledge in the art that intranasal administration of a medicament would result in greater subject compliance than intragastric administration.

***Conclusion***

5. No claim is allowed.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to F. Pierre VanderVegt whose telephone number is (571) 272-0852. The examiner can normally be reached on M-Th 6:30-4:00; Alternate Fridays 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

F. Pierre VanderVegt, Ph.D.
Patent Examiner
March 8, 2004

Christina Chan
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SUPERVISORY PATENT EXAMINER
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